EVALUATION OF THYROID FUNCTION IN CRITICALLY ILL AND SEVERELY MALNOURISHED CHILDREN

THESIS
FOR

DOCTOR OF MEDICINE
(PAEDIATRICS)

BUNDELKHAND UNIVERSITY
JHANSI(U.P)

2005 MOHD.NASIR ANSARI

DEPARTMENT OF PAEDIATRICS
M.L.B. MEDICAL COLLEGE JHANSI (U.P.)

CERTIFICATE

This is to certify that the work entitled "EVALUATION OF THYROID FUNCTION IN CRITICALLY ILL AND SEVERELY MALNOURISHED CHILDREN" has been carried out by Dr. Mohd. Nasir Ansari in the Department of Paediatrics M.L.B. Medical College, Jhansi.

He has been put in the necessary stay in the department as per university regulations.

Dated: 10/11/04

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Nasir

Dated: *Mohd. Nasir Ansari*

CONTENTS

INTRODUCTION

INTRODUCTION

Abnormalities in thyroid hormone economy occurs in ill patients, malnourished patients and patients undergoing surgery etc.

All these insults influence every aspect of thyroid hormone economy from the control of secretion to the delivery, metabolism and ultimate action. Most consistent abnormalities are in the transport and peripheral metabolism of the thyroid hormones and in their total and free concentrations in the blood. This has led to the condition known as "sick euthyroid syndrome" which is characterized by significant decrease in serum triiodothyronine (T_3), slight decrease in serum thyroxin (T_4), increase in reverse T3 level and no significant change in thyroid stimulating hormone (TSH) level.

Hormones are important in the adaptive metabolic processes. However circulating levels of hormones do not always explain endocrine changes in PEM, because cellular response to hormonal stimulation may also be altered. There are changes in serum level of insulin, growth hormone, somatomedins (insulin like growth factor), epinephrine, glucocorticoids , renin, aldosterone, thyroid hormones and gonadotropins. They contribute to the maintenance of energy homeostasis through increased glycolysis and lipolysis, increased aminoacid mobilization preservation of visceral proteins, through increased break down of muscle proteins, and decreased energy metabolism.

Thyroid gland is the sole source of T_4, but most of the T_3 in blood is derived from the peripheral conversion of T_4 by 5' deiodinase. Both T_3 and T_4 in blood are associated with plasma

proteins. The binding proteins normally include thyroxine – binding globulin, thyroxine binding pre albumin (TBPA) and albumin. In children with PEM concentration of all three thyroid hormone-binding proteins are extremely low and the serum T_4 and T_3 levels decline abruptly, often into hypothyroid range. However serum TSH concentration remains unchanged.

All non-thyroid illness in which sick euthyroid syndrome has been documented have nothing more in common than catabolic state. Hence, it has been suggested that the decrease in thyroid hormone level may be a protective phenomenon to limit protein catabolism and lower energy requirements in non-thyroidal illness. The length of time required for the development of and recovery from the sick euthyroid syndrome are less well appreciated. But the degree to which thyroid functions are affected by non-thyroid illness is related to the severity of the illness and can severe as a useful, if relatively non-specific, prognostic indicator.

In adults in different studies significant correlation of serum T_3 and T_4 levels and patient prognosis, has been shown and mortality is significantly higher in patients of non-thyroid illness with low T_4 and progressively declining T_3 levels.

However in children and especially in infants no definite correlation has yet been found. If the correlation can be established, children with a poor prognosis (low T_3, T_4 levels) could be identified earlier and this may allow for closer observation and therapeutic intervention. Keeping these objectives in mind, this study was planned.

AIMS

&

OBJECTIVES

AIMS AND OBJECTIVES

This study will carry out with the following aims and objectives

1. To estimate T_3, T_4 and TSH in critically ill children.
2. To assess thyroid hormone status in severely malnourished children.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The thyroid gland as a distinctive histologic entity found only in vertebrates.

The universality and persistence of thyroid gland through all evolutionary changes in the vertebrate series certainly indicates a functionally important role.

Thyroid gland was the first endocrine gland to be recognized as such by those symptoms with excess or deficient function in mid ninteenth century.

With the advent of radioactive iodine, physiological investigations, first by Goshman (1955) and later by Leloup, Barrington and Sage, Roche et al and Clements Merlini, sought to elucidate the interrelation between endostyle and thyroid in terms of control of biochemical functions of the thyroid gland.

Brent and Herrhman studied effects of thyroxin therapy on patients with severe non thyroid illness and low serum thyroxine concentration. Thyroxin administration rapidly normalized serum T_4 concentration but T_3 concentration did not increase. Thyroxin therapy in the said study did not augment thyroid hormone action nor did it improve survival. Decreased conversion of T_4 to T_3 in the periphery has been postulated to be the predominant cause of low T_3 levels inspite of T_4 therapy.

Mc Larty et al (1975) in a study of 30 patients of myocardial infarction showed a sequential and progressional fall in serum T_3 and T_4 levels from the time of admission reaching abnormally low in all sick patients, who died in their series.

Eisenberg et al (1980) studied a group of seventy-three patients within 48 hours of admission to the intensive care unit. They found that non survivors had a greater prevalence of decreased serum total T_4 and total T_3 than survivors.

Kaptein et al (1981) evaluated the prevalence and prognostic relevance of alterations in thyroidal indices prospectively in 195 patients requiring intensive medical therapy and in 75 critically ill patients with serum total T_4 levels below 3 μg/dl. In 195 patients, serum total T_3 and total T_4 levels were reduced in 69% and 43% respectively. Decreased total T_4 levels had the highest correlation with mortality ($P<0.001$) and correctly predicted outcome in 70% of patients. Other thyroidal indices, which were significantly different between survivors and non-survivors, correlated with total T_4 and did not contribute independently to prediction accuracy when assessed by discriminant function analysis.

Becker et al (1982) randomized burn patients with the sick euthyroid syndrome to receive either T_3 or placebo therapy. T_3 treatment did not alter mortality. The sick euthyroid syndrome accompanying starvation has a protein sparing effect. Administration of exogenous T_3 to prevent the fall in serum T_3 with fasting results in increased muscle protein breakdown, increased gluconeogenesis, and increased fat catabolism. There are no data to support routine thyroid hormone treatment of patients with the sick euthyroid syndrome.

Slag M F, Morley JE, Elson MK et al (1981) measured thyroid function in 86 patients hospitalized in an intensive care unit. They

found hypothyroxinemia with normal thyroid stimulating hormone in 22% of the patients, and was associated with high mortality.

T_4 levels	**mortality**
<3.0μg/dl	84%
3.0-5.9μg/dl	50%
>5.0 μg/dl	15%

There was a high correlation between low T_4 levels and mortality.

J.N. Carter, JM Corcoran et al (1974) detected striking abnormality in 75 sick euthyroid patients. There was a highly significant reduction in the mean free serum triiodothyronine levels with most patients having total T_3 levels in the hypothyroid range. The severity of the illness correlated well with the reduction in total serum T_3 levels. The mean free serum T_3 concentration was significantly lower than in the control patients. The mean total serum thyroxin (T_4) levels were also significantly reduced, although unlike the total serum T_3 levels they remained within the normal range. The total serum T_4 /T_3 ratios were generally higher in the sick euthyroid patients compared with the controls. Serum TSH was not increased in any patients.

J.N. Carter , C.J. Eastman et al (1976) studied to elucidate the Mechanism of low circulating T_3 Concentrations . The disappearance rate of I^{125}-T_3 from the circulation of five representative sick euthyroid patients were studied and found to be slower, but not significantly so, compared with three control subjects, thus excluding an increased destruction rate as the cause of low T_3 levels.

Decreased monodeiodination of T_4 to T_3 in sick euthyroid patients was confirmed by paper chromatography of extracted serum obtained 48 hours after an i.v. Injection of ^{125}I-T_4 into two severely ill patients from the intensive therapy unit and a control subject. Peaks of radioactivity corresponding to ^{125} I-T_4 and ^{125} I-T_3 were detected in the control subject, but only a single peak corresponding to ^{125} I-T_4 was detected in the ill patients.

Aaron R. Zucker et al (1985) studied I9 children admitted to the ICU. Approximately 24 hours after admission to the ICU, patients had a mean serum T_4 concentration of 6.4 $\pm$ 1.1 μg/dl (normal 4.2 to 11.8 μg/dl in the age range of patients studied) and mean serum T_3 of 74.4 $\pm$ 22.7 ng/dl (normal 80 to 210 ng/dl in the age range of patients studied). Six of nine patients had both serum T_4 and T_3 levels below normal for age despite basal serum TSH levels of <2.5 μlu/ml (normal < 6μl*u*/ml in the age range of patients studied).

N. Uzel and O. Neyzi (1986) investigated thyroid functions in critical illness in infancy. Serum thyroxine (T_4), triiodothyronine (T3) and thyroid stimulating hormone (TSH) concentrations were measured in 13 such patients. Significantly lower initial and subsequent T_4 values were found in the fatal group as compared with the control group. Initial T_3 concentrations both in fatal cases and in patients who recovered were significantly lower than those in the controls. Subsequent T_3 values in the group who recovered showed a relative increase, but in the fatal cases a further decrease in T_3 levels accompanied by a decrease in rT_3 levels to values comparable to those of the controls, was observed in the terminal stage.

N.K. Anand , RSK Sinha, Harish Chellani (1994) studied 30 infants with severe acute systemic illness and 30 healthy controls age and sex matched. Their T_3, T_4 and TSH levels were measured at admission and recovery or before death. They found that serum T_3 levels in infants were significantly lower than the controls with normal T_4 and TSH levels at admission. Both serum T_3 and T_4 levels increased with recovery. It was also noticed that T_3 and T_4 values were significantly reduced at or near death when compared with the admission levels.

Stirling (1962) worked on the thyroid in malnutrition. He observed that the average weight of the thyroid is lower in the Jamaican than in the British and American infants.

Francisco Beas, F Monckeberg et al (1966) worked on the thyroid response to TSH in a group of 16 patients with severe marasmus and 9 normal controls of the same age. The radioiodine uptake and the oxygen consumption were determined in both groups before and after administration of a single dose of TSH. The results suggested that the low function of thyroid gland found in marasmic infants were not only due to a decrease of TSH but also a deficit of thyroid function per se.

Graham et al (1973) had studied the thyroid hormone levels in nutritionally normal infants and in infants with marasmus on marsmic kwarshiorkor . In their study, in the normal subjects, serum thyroxine was higher during the first year of life than at birth or after one year. Free thyroxine was higher at 2to3 months of age than later. TBG decreased slightly but not significantly with age. Elevated TSH of cord serum decreased to normal adult levels by 2 to3 months. Despite

normal TBG, serum thyroxine may be decreased in marasmus and during recovery. Free thyroxine may be high to low initially and normal or low during recovery, serum TSH was low or normal at both times. In Kwashiorkor, low TBG accounts for low thyroxine but free thyroxine was normal or elevated, TSH was normal. During recovery, TBG returned to normal but thyroxine only partially elevated and free thyroxine decreased as did TSH.

Ingenbleek, M.D, Ph.D. and Paul Malvaux, M.D. Ph. D. (1980) studied the peripheral turnover of thyroxine and related parameters in infants of protein caloric malnutrition. The biological half life of thyroxine (T_4) in a group of seven protein calorie malnourished children maintained under steady state conditions was significantly increased as compared with that of seven healthy counter parts (T ½ = 2.15$\pm$ 0.19verses 3.19$\pm$ 0.33 days, P <0.001). As a result, the daily fractional turnover rate of T_4 was significantly increased at the acute stage of the disease (K=32.4$\pm$ 2.9% verses 17.8$\pm$16% /day, P<0.001). The related parameters, namely T_4 distribution space (TDS=1.21$\pm$0.16 verses 1.75$\pm$0.21 liters) extrathyroidal T_4 pool (ETP = 52.5$\pm$ 1.3 verses 1.81$\pm$ 15.7 μg T_4) and T_4 degradation rate (TDR = 16.8$\pm$2.5 verses 32.0$\pm$1.8μg T_4 / day) were significantly depressed in protein calorie malnourished children compared with healthy children (P<0.001).

W. John Kalk , Karen J Hofman et al. (1986) studied 15 infants with severe protein energy malnutrition as a model of nutritional nonthyroidal illness. Changes in circulatory thyroid hormones, binding proteins and their interrelationship were assessed before and during recovery. Serum concentrations of total thyroxine and

taiiodothyronine and of thyroxine – binding proteins were extremely reduced, It was concluded that there was reduced binding of T_4 and T_3 to TBG in untreated PEM, which takes 2-3 week to recover. Increased TSH secretion appears to be an integral part of recovery from PEM.

Turkay's et al (1995) observed the effect of protein energy malnutrition in children on serum levels of total thyroxine (T_4), total triiodothyronine (T_3) and thyrotropin (TSH). There were 107 children of 2 to 60 months in the malnutrition group and 54 healthy age and sex matched control. Serum $TT_4$and TT_3 were all reduced in the malnutrition group. This decrease in TT_3 was more significant ($P<0.01$) in severe malnutrition than in mild PEM .Serum TSH levels in the malnutrition and control groups were similar. These results suggest that the children remained euthyroid and represent an adaptive response to protein energy malnutrition.

Orbak et al (1998) investigated the effect of malnutrition on thyroid gland weight and thyroid hormone levels. 22 children suffering from malnutrition (14 children suffering from marasmus and 8 children suffering from kwashiorkor) and 7 healthy control were studied. Malnutrition was confirmed clinically and according to the welcome trust classification. Serum thyroid hormone concentrations were measured by radioimmunoassay and weight of thyroid gland were evaluated scintigraphically . In the group with marasmus and kwashiorkor, the mean TT_4, TT_3 and FT_4 levels were significantly lower and TSH levels were significantly higher, compared to control. FT_4 was not influenced by PEM . The mean thyroid gland weights of

the group with marasmus and kwashiorkor were higher than that of the control groups.

Das MD et al (1999) worked on thyroid hormone in protein energy malnutrition. The mean serum triiodothyronine and free T_3 (FT_3) levels were significantly lower in malnourished children, whereas the total thyroxine (TT_4) free T_4 (FT_4) and thyroid stimulating hormone (TSH) levels were in the normal range.

Verma et al (2000) studied the effect of protein energy Malnutrition on serum levels of T_3, T_4 and TSH. A total of 100 children of 1-4 year's of age group were included in the study, of which 20 healthy children with age and sex matched acted as control, 80 children were graded into four groups as per Indian academy of pediatrics (IAP) classification of PEM. Patients with infections were excluded from the study.

Serum T_3 and T_4 levels were reduced in all grades of Malnutrition group. This decrease in T_3 level was significantly low in grade II-IV (grade II $P< 0.05$ III &IV $P<0.001$). In grade I PEM, decrease in serum T_3 was not significant. Serum T_4 levels were decreased significantly in all grades of PEM (in grade I and II $P< 0.05$, grade III $P< 0.01$ grade IV $P<0.001$). Serum TSH levels in Malnutrition and control group was similar.

These results suggests that the children in Malnutrition group remained euthyroid and decrease in thyroid hormone levels, probably an adaptive change to PEM, which enable the sick patient to conserve protein.

MATERIAL & METHODS

MATERIAL AND METHODS

The study was conducted in the department of paediatrics with collaboration of department of microbiology M.L.B. Medical College, Jhansi.

SELECTION OF CASES: -

Study subjects comprised of children in age group of one month to 48 months suffering from severe systemic illness requiring intensive care.

Another group of patients consists of children weighting less than 50% of 50^{th} percentile of Howard standard for their age. The cases of PEM were graded according to classification adopted by Indian academy of paediatrics.

The weight of patient was recorded nearest to 0.05 kg, by using infant weighting scale for weight of less than 10 kg, while adult type weighting machine was used in children weighting more than 10 kg, in the later weight was recorded nearest to 0.1kg.

SELECTION OF CONTROL:

Healthy children who matched for age and sex were taken from children of normal weight for age attending hospital for either checkup for minor ailments or brother and sister of patients admitted in the paediatric ward.

All children with maternal history of thyroid dysfunction, children with clinical evidence of endocrine abnormality, especially thyroid and infants with clinical goiter were excluded from the study.

All the cases were subjected to: -

1. Detailed history regarding illness, relevant past history, family history, birth history and mile stones.
2. Thorough clinical examination including anthropometric measurements.
3. Routine investigations and specific investigations as per requirement of illness.
4. Estimation of serum thyroid hormones.

Specimen collection and preparation:-

For estimation of thyroid hormones, about 5 ml of blood was collected in plain vial without any additive through venipuncture after full aseptic precaution and blood was allowed to clot and serum was separated immediately by centrifugation.

Samples were stored for short time (up to 48hrs) at 2-8^{0}C and for extended storage (up to 30 days) at – 20^{0}C. Grossly hemolyzed, contaminated, lipemic samples and highly icteric samples were avoided. Repeated freezing and thawing were avoided. In case of frozen samples it was made sure to thaw samples completely before use.

Estimation of serum thyroid hormones by ELISA method

Principle of estimation of triiodothyronine (T_3) and thyroxine (T_4)

The ELISA test was performed as a solid phase competitive immunoassay. Microwells are coated with anti-T_3/T_4 antibody,

followed by blocking the unreacted sites to reduce non-specific bindings.

Step I – T_3/T_4 antigen, present in samples and standards, and a fixed amount of T_3/T_4 conjugated with Horseradish Peroxidase compete for the binding sites of antiT_3/T_4 polyclonal antibodies coated onto the wells.

Step 2- the conjugated enzyme converts added substrate (TMB) to form a colored solution.

Step3 – The intensity of color change, which is inversely proportional to the concentration of T_3/T_4 in the samples are read by a microplate reader at 450 nm.

Results are expressed in ng/dl in case T_3 and μg/dl in case of T_4.

Principle of estimation of serum thyroid stimulating hormone (TSH)

The ELISA is performed as an indirect solid phase sandwich – type immunoassay, streptavidin – Boitin Method.

Step 1- Antigen present in controls, calibrators and patient sample binds to polyclonal anti TSH Enzyme labeled antibody and which vise versa binds irreversibly to the streptavidin–coated wells. The Bontinylated–Enzyme labeled antibodies exhibit different and distinct epitope recognition, reaction results between native antigen and the antibodies without competition or steric hindrance to form a soluble sandwich complex.

Step 2- The conjugated Enzyme converts added substrate (TMB) to from a colored solution.

Step 3- The intensity of color change, which is proportional to the concentration of TSH in the sample is read by a microplate reader at 450 nm. results are expressed in μlu/ml.

REAGENT PREPARATION

1. Wash Buffer

Wash buffer concentrate was diluted a final volume of 1000ml with distilled water in a suitable container prior to use.

2. Working reagent 1- T_3/T_4 Enzyme Conjugate solution

Triiodothyronine–enzyme conjugate or thyroxine enzyme conjugate was diluted with triiodothyronine enzyme conjugate buffer or thyroxine enzyme conjugate buffer respectively in ratio of 1:11 in suitable container. For example - 160 μl conjugate diluted with 1.6 ml of buffer for 16 wells (a slight excess of solution was made). This reagent was used within 24 hours for maximum performance of the assay.

General Formula:-

Amount of buffer required = Number of well x 0.1

Quantity of enzyme conjugate necessary = # of wells 0.01

i.e. = 16X0.1=1.6 ml enzyme conjugate buffer.

16X0.01=0.16 ml (160μl) for enzyme conjugate.

3. Working Substrate Solution

Amount or reagent needed was determined and prepared by mixing equal portions of substrate A and substrate B in a suitable container. For example, 1ml of A and 1 ml of B were added per eight well strips (A slight excess of solution was made). This working

substrate solution prepared was used with in one hour for maximum performance of assay.

TEST PROCEDURE

Before proceeding with the assay, all the reagents and specimens brought to room temperature (20-27^{0}C).

1. Wash buffer was prepared.
2. Working reagent 1-T_3/T_4 – enzyme conjugate solution was prepared.
3. Working substrate solution was prepared immediately before use.
4. Microplate wells for each serum reference, control and patient specimen were assayed in duplicate. Unused microwell strips were replaced back into the sealed pouch and stored at-20^{0}C.
5. 50 µl for T_3 and TSH and 25 µl for T_4 of the appropriate serum reference, control or specimen was pipetted into the assigned well.
6. 100µl of conjugate was added to each well, bubble formation was avoided.
7. The plate was shaked thoroughly for 20-30 seconds.
8. Above microplate wells were incubated for 60 minutes for T_3 and T_4, and 120 minutes for TSH at room temperature.
9. Contents of the microplate wells discarded by decantation or aspiration. Then plates were dried by tapping and blotting with absorbent paper.
10. 300µl of wash buffer was added, decanted or aspirated. This procedure was repeated two additional times for a total of three (3) washes. A manual plate washer was used.

11. 100μl of working substrate solution was added to each well in the same order and timing of the conjugate.
12. Microplate wells were incubated at room temperature for fifteen(15) minutes.
13. 50μl stop solution was added to each well using the same order and timing as for the addition of the enzyme substrate.
14. Absorbance was read in each well at 450 nm in a microplate reader. The results were read within thirty (30) minutes of adding the stop solution.

Results

A dose response curve was used to ascertain the concentration of T_3/T_4 and TSH levels in unknown specimens.

1. Absorbance was recorded from the printout of the microplate reader.
2. Absorbance were plotted for each serum references, versus the corresponding T_3, T_4 and TSH concentrations in ng/dl for T_3,μg/dl for T_4 and μlu/ml for TSH on a linear graph paper.
3. Best – fit curve was drawn through the plotted points.
4. For determining the concentrations of T_3,T_4 & TSH for unknown, the average absorbance of the cases was located on the vertical axis of the graph and the intersecting point was obtained on the curve , and the concentration was read from the horizontal axis of the graph .

Limitations of the procedure

The assay should not be performed on grossly hemolyzed, microbially contaminated or lipemic samples.

OBSERVATIONS

OBSERVATIONS

The present study entitled "Evaluation of thyroid function in critically ill and severely malnourished children" was performed in the Department of Pediatrics, M.L.B. Medical College, Jhansi with collaboration of Department of Microbiology, M.L.B. Medical College, Jhansi over a period of one year.

Total 50 cases were included in the present study. Study subjects comprised of children in age group of one month to 48 months.

TABLE –1

STUDY AND CONTROL GROUPS

	Control Group	Study Group	
		Critically Ill Patients	Severely Malnourished Patients
No. of cases	10	20	20

Cases were divided into 3 groups. Group one comprised of critically ill children. Twenty cases of critically ill children were included in the study. These children were suffering from acute severe systemic illnesses like patients with cardiovascular compromise (shock, hypotension, hypertensive crisis), acute neurological deterioration (coma, status epilepticus, increased I.C.T.), respiratory impairment or failure , acute renal failure , bleeding disorder that necessitate massive transfusion. .

Another group of patients consists of children weighting less than 50% of 50th percentile of Howard standard for their age. The cases of PEM were graded according to classification adopted by Indian academy of paediatrics. 20 cases of severely malnourished children were included in the study.

Control group comprised of 10 healthy children who matched for age and sex, were taken from children of normal weight for age attending hospital for checkup.

All children with maternal history of thyroid dysfunction, children with clinical evidence of endocrine abnormality, especially thyroid and infants with clinical goiter were excluded from study.

TABLE –2

AGE DISTRIBUTION OF CASES

Age in Years	Critically ill patients		Severely Malnourished Patients	
	No. Cases	**Percentage**	**No. Cases**	**Percentage**
0-1	07	35%	06	30%
1-2	08	40%	08	40%
2-3	03	15%	04	20%
3-4	02	10%	02	10%

Table 2 depicts the number of cases taken for the present study according to age group.

Among critically ill patients 35% of cases were under 1 year of age, 40%of cases were 1to 2 years of age, 15% of cases were 2 to 3 years of age and 10% of cases were 3 to 4 years of age.

Among severely malnourished patient 30% of cases were under 1 year of age, 40% of cases were 1 to 2 years of age, 20% of cases were 2 to 3 years of age and 10% of cases were 3 to 4 years of age.

TABLE - 3

SEX DISTRIBUTION OF CASES

Clinical Forms	Sex			
	Boys		Girls	
	No.	Percentage	No.	Percentage
Critically Ill Patients	15	75%	05	25%
Severely Malnourished patients	08	40%	12	60%
Control	06	60%	04	40%

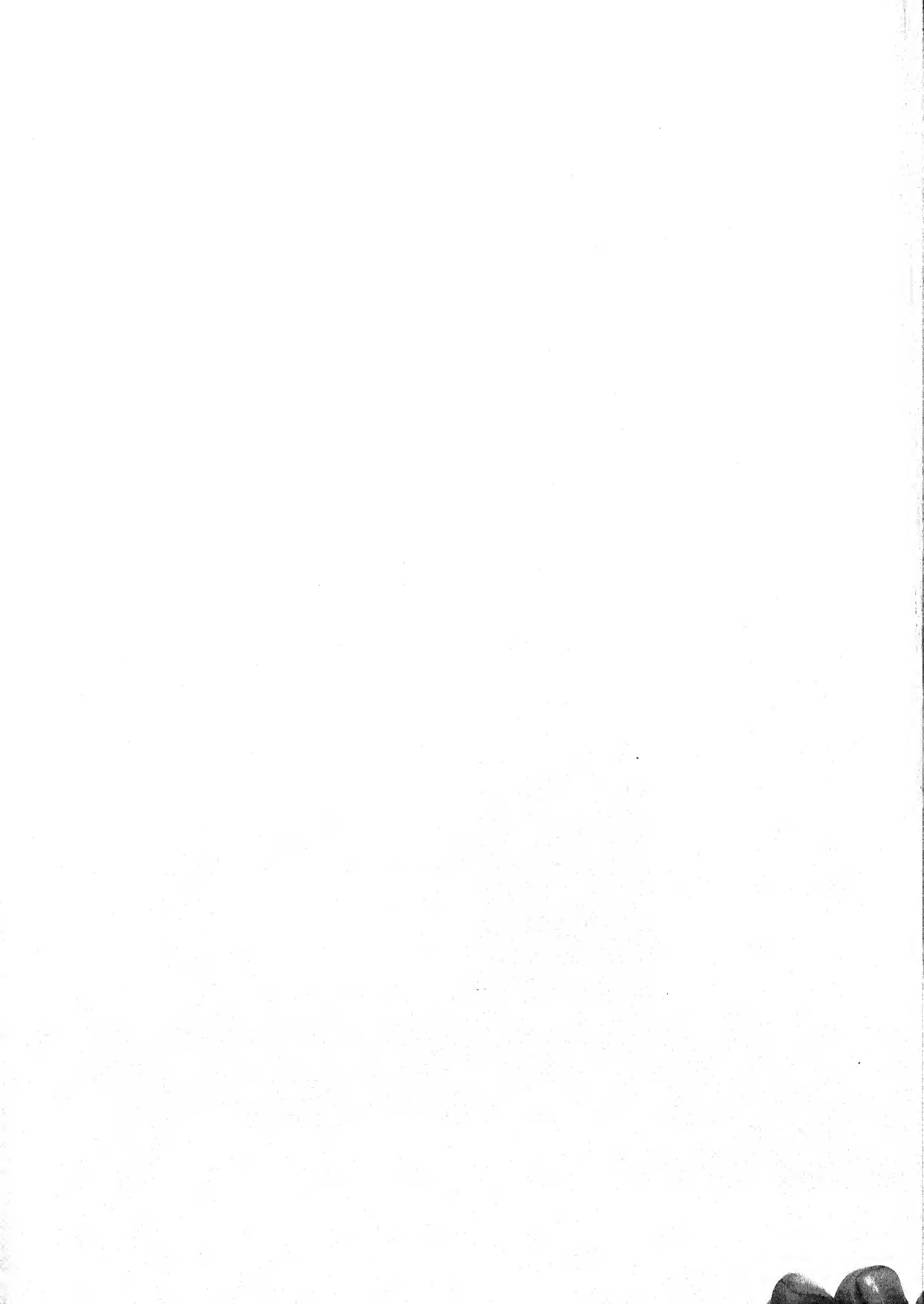
Table 3 shows number of cases in the study and control group divided according to sex of patients.

There were 23 males and 17 females in study group, and 6 males and 4 females in control group.

Amongst the critically ill patients group, there were 15 (75%) males and 5 (25%) females.

Amongst the severely malnourished patients group there were 8(40%) males and 12 (60%) females .

Amongst the control group there were 6 (60%) males and 4 (40%) females.



Mean T3 Levels (ng/dl) in control vs study group (Critically ill Patients)

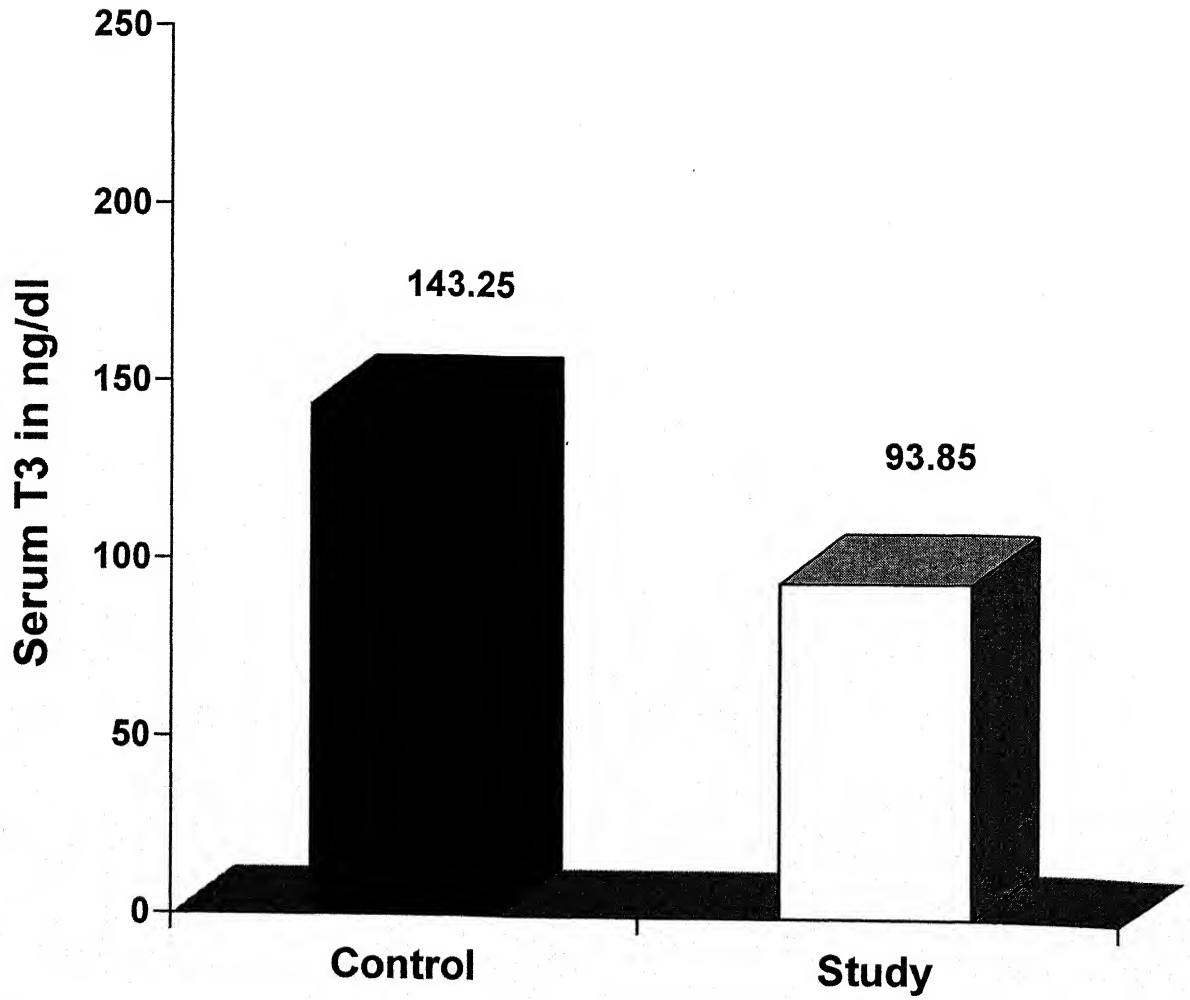


TABLE -4

MEAN VALUES OF SERUM T_3, IN CRITICALLY ILL PATIENTS AND CONTROL GROUP

GROUP	No. of Cases	Serum T3 ng/dl	
		Range	Mean ± S.D.
Critically ill patients	20	56-150	93.85±22.26
Control Group	10	101-197	143.25±31.76

Statistics of serum T_3 in critically ill patients versus control group.

t-value	d-f	P value	Statistical significance
4.9633	28	<.001	Highly significant

Table 4 shows the mean, standard deviation and range of total serum T_3 in ng/dl in the control and study group cases. In control group cases total serum T_3 level was 143.25± 31.76 ng/dl with a range of 101-197 ng/dl. In the study group, total serum T_3 level was 93.85 ± 22.26 ng/dl with a range of 56-150 ng/dl.

On statistical analysis it was observed that the levels of total serum T_3 was found to be significantly lower in study group cases in comparison to control group cases (P<. 001).

Mean T3 Levels (ng/dl) in control vs study group (Severely Malnourished Patients)

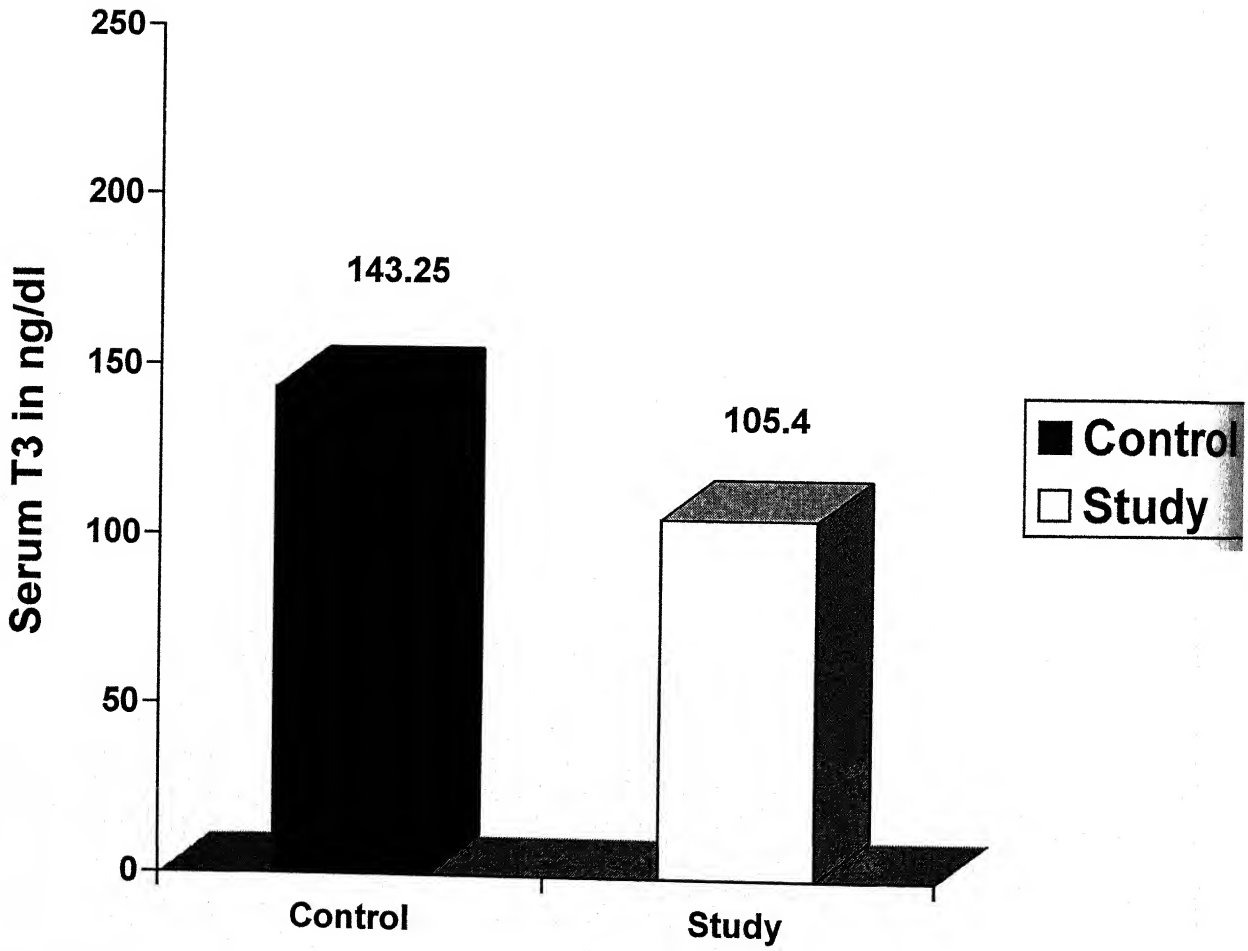


TABLE –5
MEAN VALUES OF SERUM T_3 IN SEVERELY MALNOURISHED PATIENTS AND CONTROL GROUP

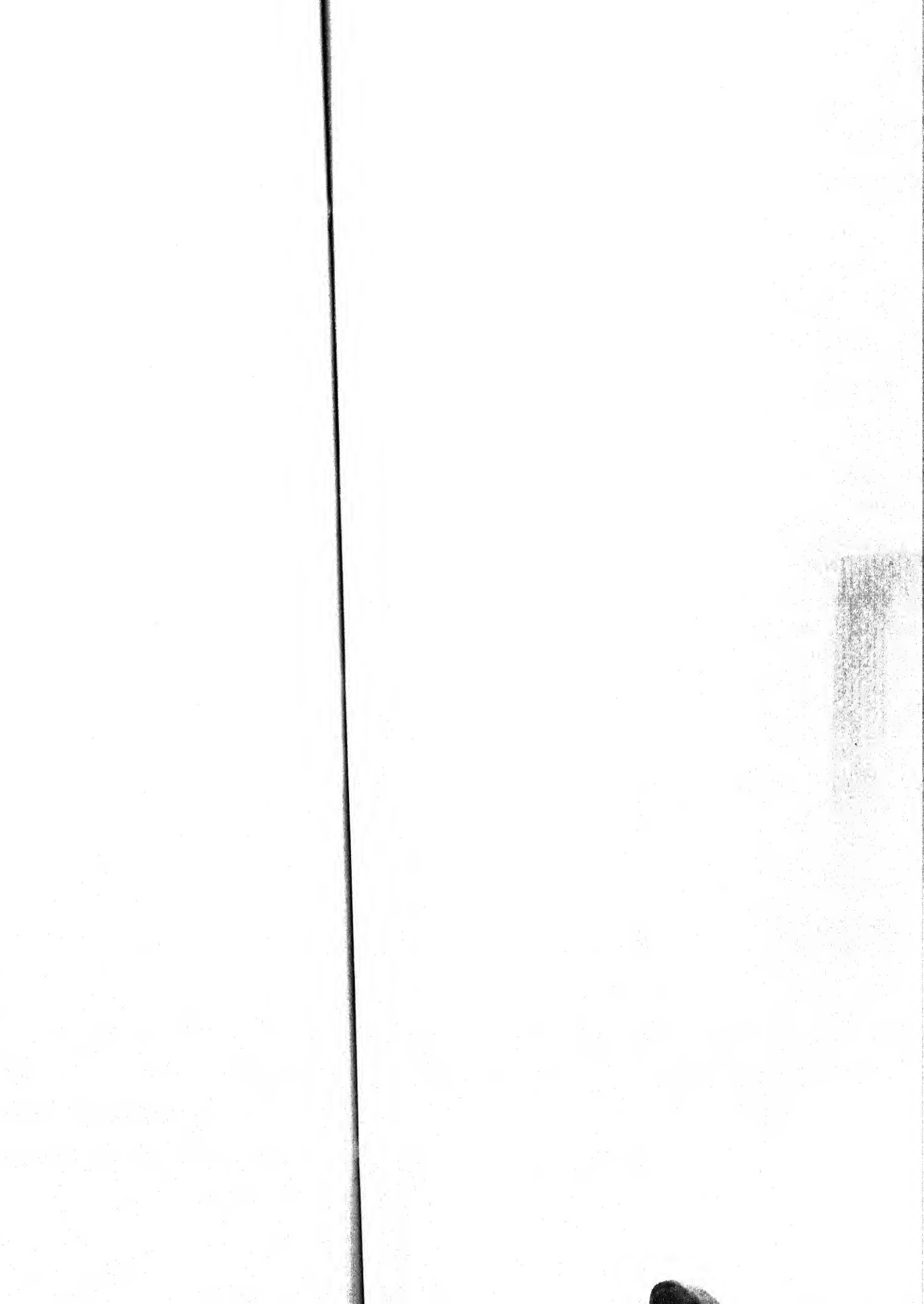
GROUP	No. of Cases	Serum T3 ng/dl	
		Range	Mean ± S.D
Severely Malnourished patients	20	59-172	105.40±36.26
Control Group	10	101-197	143.25±31.76

Statistics of serum T_3 in severely malnourished patients versus control group.

t-value	d-f	P value	Statistical significance
2.802	28	<.01	significant

Table 5 shows the mean, standard deviation and range of total serum T_3 in ng/dl in the control and study group cases. In control group cases total serum T_3 level was 143.25± 31.76 ng/dl, with a range of 101-197 ng/dl. In the study group, total serum T_3 level was 105.40±36.26 ng/dl with a range of 59-172 ng/dl.

On statistical analysis it was observed that the levels of total serum T_3 was found to be significantly lower in study group cases in comparison to control group cases (P<. 01).



Mean T4 Levels (μg/dl) in control vs study group (Critically ill Patients)

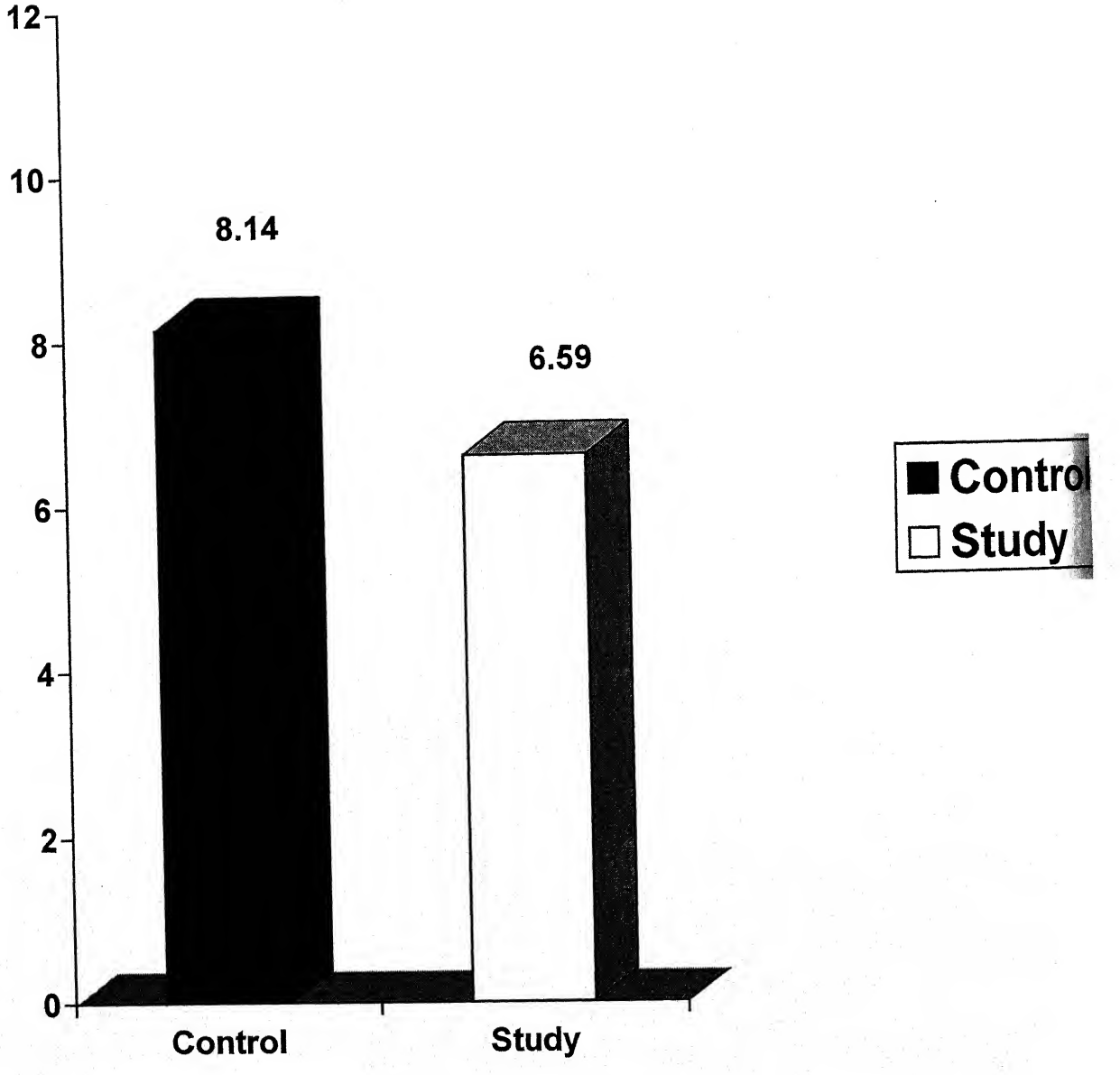


TABLE –6

MEAN VALUES OF SERUM T_4 IN CRITICALLY ILL PATIENTS AND CONTROL GROUP

GROUP	No. of Cases	Serum T_4 μg/dl	
		Range	Mean ± S.D
Critically ill patients	20	4.21-9.62	6.59±1.60
Control Group	10	6.98-9.11	8.14±0.67

Statistics of serum T_4 in critically ill patients versus control group.

t-value	d-f	P value	Statistical significance
2.919	28	<.01	significant

Table 6 shows the mean, standard deviation and range of total serum T_4 in μg/dl in the control and study group cases. In control group cases total serum T_4 level was 8.14±0.67 μg/dl with a range of 6.98-9.11 μg/dl. In the study group, total serum T_4 level was 6.59±1.60μg/dl with a range of 4.21-9.62 μg/dl.

On statistical analysis it was observed that the levels of total serum T_4 was found to be significantly lower in study group cases in comparison to control group cases (P<. 01).

Mean T4 Levels (μg/dl) in control vs study group (Severely Malnourished Patients)

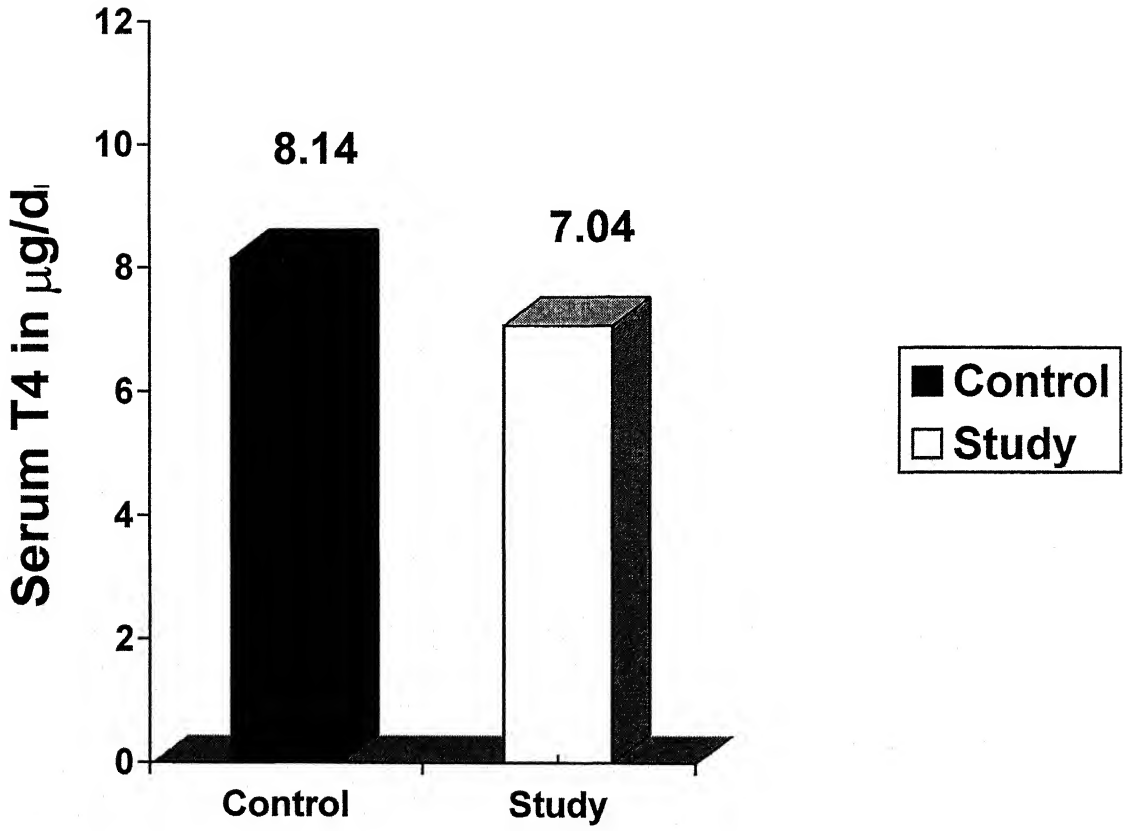


TABLE –7

MEAN VALUES OF SERUM T_4 IN SEVERELY MALNOURISHED PATIENTS AND CONTROL GROUP

GROUP	No. of Cases	Serum T_4 μg/dl	
		Range	Mean ± S.D
Severely Malnourished patients	20	5.01- 8.92	7.04± 1.26
Control Group	10	6.98-9.11	8.14±0.67

Statistics of serum T_4 in severely malnourished patients versus control group

t-value	d-f	P value	Statistical significance
2.570	28	<.02	significant

Table 7 shows the mean, standard deviation and range of total serum T_4 in μg/dl in the control and study group cases. In control group cases total serum T_4 level was 8.14±0.67 μg/dl with a range of 6.98-9.11 μg/dl. In the study group, total serum T_4 level was 7.04±1.26 μg/dl with a range of 5.01-8.92 μg/dl.

On statistical analysis it was observed that the levels of total serum T_4 was found to be significantly lower in study group cases in comparison to control group cases (P<. 02).

Mean TSH levels in Control vs study group (Critically ill patients)

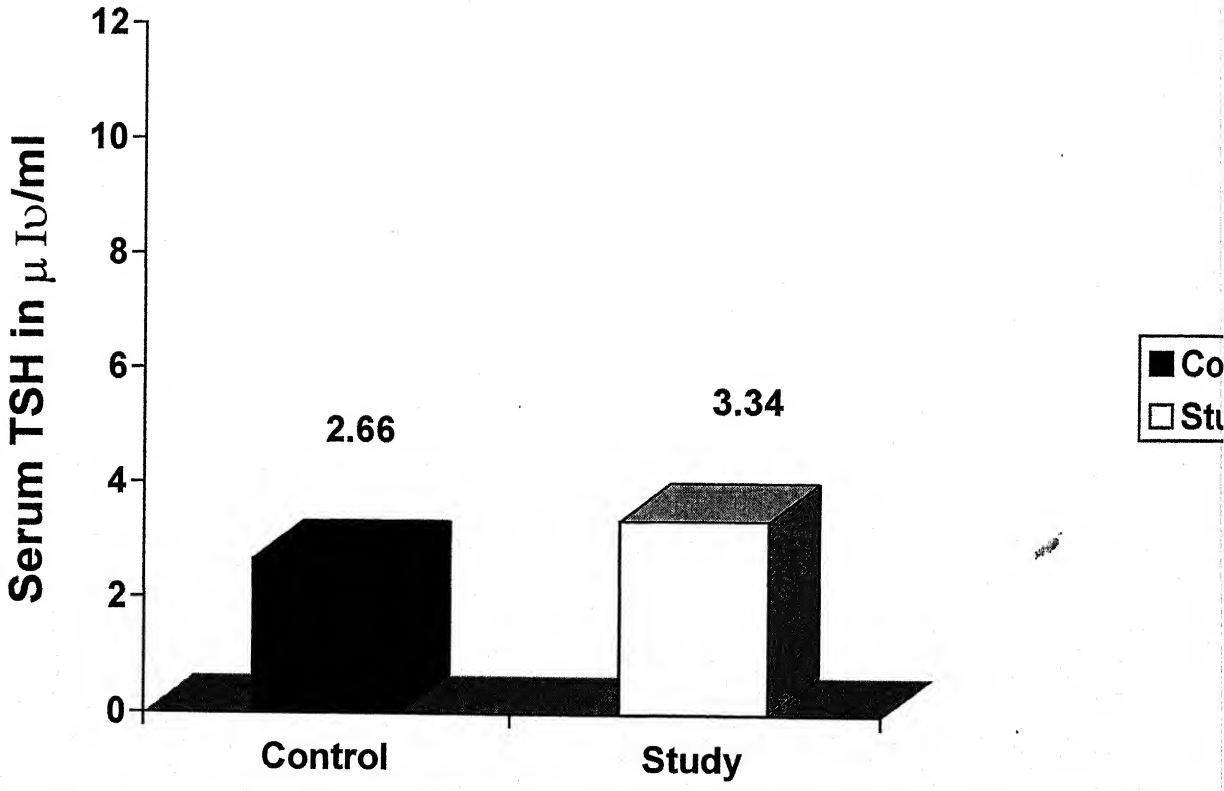


TABLE –8

MEAN VALUES OF SERUM TSH IN CRITICALLY ILL PATIENTS AND CONTROL GROUP

GROUP	No. of Cases	Serum TSH μlu/ml	
		Range	Mean ± S.D
Critically ill patients	20	1.42-5.10	3.34±1.10
Control Group	10	1.36-4.51	2.66±0.89

Statistics of serum TSH in critically ill patients versus control group.

t-value	d-f	P value	Statistical significance
1.695	28	>.10	Not significant

Table 8 shows the mean, standard deviation and range of serum TSH in μlu/ml in the control and study group cases. In control group cases serum TSH level was 2.66±0.89 μlu/ml with a range of 1.36-4.51 μlu/ml. In the study group, serum TSH level was 3.34±1.10 μlu/ml with a range of 1.42-5.10 μlu/ml.

On statistical analysis it was observed that the levels of serum TSH was not found to be significantly higher in study group cases in comparison to control group cases (P>.10).

Mean TSH levels in Control vs study group (Severely Malnourished Patients)

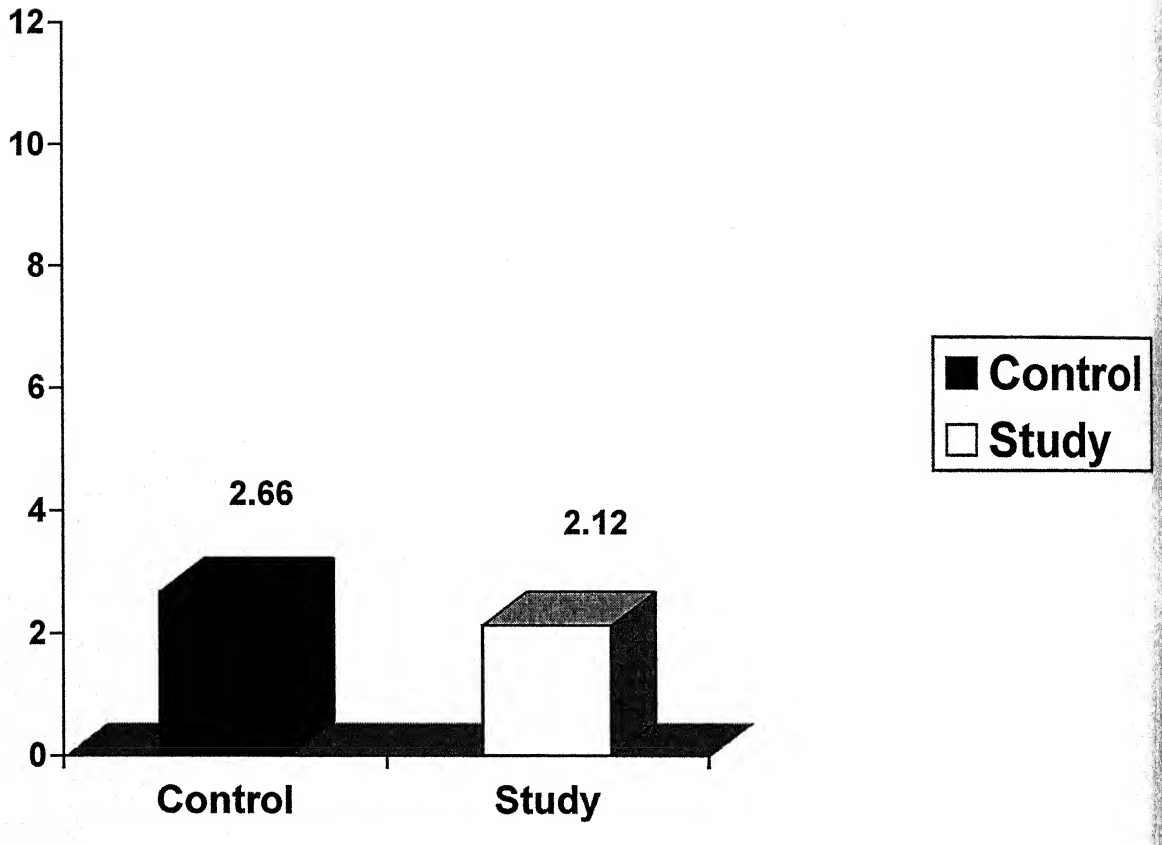


TABLE –9

MEAN VALUES OF SERUM TSH IN SEVERELY MALNOURISHED PATIENTS AND CONTROL GROUP

GROUP	No. of Cases	Serum TSH μlu/ml	
		Range	Mean ± S.D
Severely Malnourished patients	20	1.77-4.12	2.12± 0.84
Control Group	10	1.36-4.51	2.66±0.89

Statistics of serum TSH in severely malnourished patients versus control group.

t-value	d-f	P value	Statistical significance
1.636	28	>0.1	Not significant

Table 9 shows the mean, standard deviation and range of total serum TSH in μlu/ml in the control and study group cases. In control group cases total serum TSH level was 2.66±0.89 μlu/ml with a range of 1.36-4.51 μlu/ml. In the study group, total serum TSH level was 2.12±0.84 μlu/ml with a range of 1.77-4.12 μlu/ml.

On statistical analysis it was observed that the levels of total serum TSH was not found to be significantly lower in study group cases in comparison to control group cases (P>0.1).

Our study inferred that the lower mean values of serum T_3 and serum T_4 levels were statistically significant in both critically ill patients and severely malnourished patients when compared to the control group of cases.

However it was also seen that the difference in mean values of serum TSH in study and control groups were statistically insignificant in both critically ill patients and severely malnourished patients.

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DISCUSSION

DISCUSSION

There are two thyroid hormones with biologic activity in vivo one of them, thyroxine (T_4) is produced only by the thyroid gland. The other 3,5,3' - Triiodothyronine (T_3) is produced largely by deiodination of T_4 at extrathyroidal sites and the thyroidal contribution to over all T_3 production is small. The recognition that T_3 , the more potent of the two hormones, is produced outside the thyroid gland has changed the way that thyroid hormone production and its regulation must be viewed. Thyroid hormone production is not simply dependent on normal hypothalmic- pitutary - thyroid function.

Under normal circumstances 100% of T_4 and 10-20% of T_3 in the serum is directly secreted by the thyroid gland. The remaining 80% of the T_3 is derived from peripheral monodeiodination of T_4 by the enzyme 5'deiodinase.

In adults and in children many medical and surgical illnesses lead to sick euthyroid syndrome.

Several studies have correlated both the serum T_4 and T_3 levels with increased mortality in adults but little is known in children especially in infants.

In present study the mean serum T_3 and T_4 levels of both critically ill and severely malnourished patients were significantly lower as compared to that of control group. However it was also seen that the difference in mean values of serum TSH in study and control groups were statistically insignificant in both critically ill patients and severely malnourished patients.

Our observations are consistent with that of Eisenberg et al (1980), Kapteins et al (1981), Slag MF et al (1981), JN Carter et al (1974), Zucker et al (1985) , N Uzel et al (1986) and N.K. Anand et al (1994) for critically ill patients , and Graham et al (1973), Ingenbleek et al (1980) Turkays et al (1995) and Verma et al (2000) for severely malnourished patients .

J.N. Carter et al (1974) detected striking abnormality in 75 sick euthyroid patients. There was a highly significant reduction in the mean free serum triiodothyronin levels with most patients having total T_3 levels in the hypothyroid range. The severity of illness correlated well with the reduction in total serum T_3 levels. The mean free serum T_3 concentration was significantly lower than in the control patients. The mean total serum thyroxin levels were also reduced significantly although unlike the total serum T_3 levels they remained with in the normal range. Serum TSH was not increased in any patients which is comparable to our study.

Aaron R. Zucker et al (1985) studied 9 children admitted to the ICU. Approximately 24 hours after admission to the ICU, patients had a mean serum T_4 concentration of 6.4$\pm$ 1.1 μg/dl (normal 4.2 to 11.8 μg/dl in the age range of patient studied) and mean serum T_3 of 74.4$\pm$22.7 ng/dl (normal 80- to 210 ng/dl in the age range of patient studied). Six of nine patients had both serum T_4 and T_3 levels below normal for age despite basal serum TSH levels of < 2.5 μlu/ml (normal <6μlu/ml in the age range of patient studied), which is in concordance with our study.

It can also be inferred from our observation that the patients, in whom the course of the disease was fatal, serum T_3 and T_4 levels were low as compared to patients who were discharged. This shows that there was a marked fall in serum T_3 and serum T_4 values in patients whose illness was severe enough to end in mortality. Our study had 9 patients with T_4<5 μg/dl, and six of them died.

In various studies nadir value of T_4 and T_3 or sequential decrease in the values has been correlated to mortality. Mclarty et al (1975) in a study of 30 patients of myocardial infarction showed a sequential and progressive fall in serum T_3 and T_4 levels from the time of admission reaching abnormally low in all six patients who died in their series.

Eisenberg et al (1980) studied a group of seventy-three patients with in 48 hours of admission to the intensive care unit. They found that nonsurvivors had a greater prevalence of decreased serum total T_3 and T_4 than survivors.

Slag MF et al (1981) measured thyroid function in 86 patients hospitalized in an intensive care unit. They found hypothyroxinemia with normal thyroid stimulating hormone (TSH) levels in 22% of the patients and were associated with a high mortality. There was a high correlation between low T_4 levels and mortality. Their results are comparable to our study

Kaptein et al(1980) In a study of 195 critically ill medical patients correlated clinical outcomes with the lowest of serial T_4 values as well as other thyroid indices. Mortality was inversely related to nadir serum T_4 concentration. Our study also had 9 patients with T_4<5 μg/dl, and six of them died.

N. Uzel and O. Neyzi (1986) investigated thyroid function in critical illness in infancy. Serum thyroxin (T_4), triiodothyronine (T_3), reverse triiodothyronine (rT_3) and thyroid stimulating hormone (TSH) levels were measured in 13 such patients. Significantly lower initial and subsequent T_4 values were found in the fatal group as compared with the control group. Initial T_3 concentrations both in fatal cases and in patients who recovered were significantly lower than those in the controls. Subsequent T_3 values in the group who recovered showed a relative increase, but in the fatal cases a further decrease in T_3 levels accompanied by a decrease in rT_3 levels to values comparable to those of the controls, was observed in the terminal stage.

Similarly like Uzel & Neyzi , N.K. Anand et al (1994) studied 30 infants with severe acute systemic illness and 30 healthy controls age and sex matched. Their T_3, T_4, and TSH levels were measured at admission and recovery or before death. They found that serum T_3 levels in infants were significantly lower than the controls with normal T_4 and TSH levels at admission. This is contradictory to our study and study conducted by Uzel & Neyzi in context of mean serum T_4 levels. However both serum T_3 and T_4 levels increased with recovery. It was also noticed that T_3 and T_4 values were significantly reduced at or near death when compared with the admission levels.

Graham et al (1973) had studied the thyroid hormone levels in nutritionally normal infants and in infants with marasmus or marasmic kwashiorkor. The T_4 level in the study group was 9.5 ± 0.8 μg/dl, and 4.6 ± 0.4 μg/dl in patients of marasmus and marasmic kwashiorkor respectively, which were lower than the control group (mean

12.3±0.6μg/dl). In their study they observed that despite normal TBG serum thyroxin may be decreased in marasmus and during recovery; free thyroxin may be high to low initially and normal or low during recovery; serum TSH was low or normal at both times. Their results of marasmic kwashiorker group of patients are comparable to our study.

Ingenbleek (1986) also reported that there were decreased levels of TT_4, TT3 and FT_3 in patients of PEM. Values of TT_3, TT4 and TSH in patients of PEM were 55±37 ng/dl, 3.5±1.1μg/dl and 5.4μlu/ml respectively and in control group the values of TT_3, TT_4, and TSH were 236± 41ng/dl, 8.4±1.2μg/dl and 8.2±2.7 μlu/ml respectively. FT_4 level was normal or even high in short term PEM contrasting with the decline of FT_4 to hypothyroid range in protracted PEM as result of both thyroid failure and exhaustion of liver thyroxin stores serum TSH level was normal throughout the entire course of therapy.

Turkay's et al (1995) also observed the effect of protein energy malnutrition in children on serum thyroid hormones. Serum TT_4 and TT_3 were all reduced in malnourished group. This decrease in TT_3 was statistically significant ($P<0.01$) in severe malnutrition. They also reported no change in serum TSH level in the PEM and control group as observed by us. The mean values of T_4,T_3 and TSH in their study group were 8.47±0.21 μg/dl, 139.96±3.19 μg/dl and 2.42±0.07 μlu/ml respectively , and in control group the mean values of T_4, T_3 and TSH were 9.29±0.25μg/dl , 156.87±3.50 ng/dl and 2.28±0.08 μlu/ml respectively, which is in concordance with our study.

Das M.D. et al (1999) observed that, the mean serum triiodothyronin (TT_3) and free T_3 (FT_3) level were significantly lower in malnourished children, where as the total thyroxine (TT_4) and thyroid stimulating hormone (TSH) levels were in the normal range. Their study is not correlated with present study regarding TT_4 levels.

Our study amply demonstrates that protein energy malnutrition has deleterious effect on thyroid function. Various hypotheses have been given by different authors to explain these findings. It may be attributed to impaired thyroidal secretion rate (Ingenbleek et al 1976). Low levels of thyrobinding proteins (Oppenheiner , 1968; Ingenbleek et al 1974, Pain and Phillips, 1976). Relative iodine deficiency associated high fecal loss and malabsorbtion of iodine (Ingenbleek and Backers, 1973: ingenbleck & Malvaux , 1974) or abnormal thyrotropin secretion (Pin stone et al 1973, Vinik et al 1975, Croxson et al 1977).

Low plasma TT_3 concentration may also be brought about by decreased peripheral conversion of TT_4 to TT_3. The majority of T_3 in serum arises from monodeiodination of T_4 rather than from direct thyroid secretion (Portnay et al 1974). Impaired monodeiodination of thyroxine in the liver has been suggested as a contributory factor to the reduced T_3 levels in malnutrition (Ingenbleek & Beckers, 1975).

Impaired T_4 monodeiodination in liver due to reduced activity of 5' deiodinase system resulting in a decrease in serum T_3 and increase in serum rT_3 concentrations commonly known as " low T_3 syndrome". Corticosteroids, which are elevated in stress also inhibit T_3 generation from T_4 by inhibiting the 5- deiodinase system.

Different hypotheses for decrease serum concentration of T_4 as well as T_3 have been given by different researchers viz- decreased thyroid secretion rate, decreased serum concentration of thyrobinding proteins like TBG, TBPA and serum albumin, relative iodine deficiency associated with high fecal loss and malabsorbtion of iodine and abnormal thyrotropin secretion.

Normal TSH level is explained on the basis that as T_4 undergoes intracellular monodeiodination to T_3 at the pituitary level, so central feed back mechanisms are apparently preserved, allowing appropriate adaptation of the thyroid.

The importance of changes in thyroid hormone level with non-thyroidal illness is uncertain. At present there is no evidence that T_4 administration is required in euthyroid sick syndrome. Brent and Hershman (1986) studied effects of thyroxin therapy on patients with severe NTI and low serum thyroxin concentration. Thyroxin administration rapidly normalized serum T_4 concentration but T_3 concentration did not increase. Thyroxin therapy in the said study did not augment thyroid hormone action nor did it improve survival. Decreased conversion of T_4 to T_3 in the periphery has been postulated to be the predominant cause of low T_3 levels in spite of T_4 therapy.

A very significant and an interesting observation of our study which has also been reported by other workers is that though thyroid activity is altered in patients of PEM most of the patients remain euthyroid clinically.

The findings suggested that the altered thyroid profile in critically ill patients and in PEM is perhaps a defense mechanism

against excessive metabolic stimulation and energy consumption. The resultant hypometabolism protects the malnourished child with low calorie reserve from an early death.

SUMMERY

SUMMARY

This study entitled "evaluation of thyroid function in critically ill and severely malnourished children" was undertaken with the aim to study the changes in thyroid hormonal pattern in cases of critical illness and severe malnourishment. We studied 50 cases between one month to 48 months, in which 10 cases served as control and 20 cases of critical illness and 20 cases of severe malnourishment were taken in the study group. Study subjects comprised of children suffering from acute severe systemic illness requiring intensive care and children weighting less than 50% of 50^{th} percentile of Howard standard for their age. The cases of PEM were graded according to classification adopted by Indian academy of paediatrics. Controls were age and sex matched with the study group. Details of history inclusive of present illness, past illness, birth history, dietary history, anthropometric measurements, clinical examination, biochemical analysis were secured on specially designed Performa. Patients having maternal history of thyroid dysfunction, evidence of endocrine abnormality especially thyroid and with clinical goiter were excluded from the study. Blood sample were collected in plain vial and serum was separated by centrifugation and stored at $-20^{0}C$ for up to 30 days. Samples were analysed by ELISA method for thyroid hormones.

Observations were tabulated and data was analysed statistically. The Mean $\pm$ S.D. values were calculated and statistical significance of each parameter was determined by applying students

't' test, comparing the value in study group with that of control group. The following inferences were made when data were analysed.

Evaluation of thyroid hormone status

1. **Triiodothyronine (T_3): -** The mean values of serum T_3 was lower in both study groups (93.85±22.26 in critically ill and 105.40±36.26 in severely malnourished patients) as compared to that of control group (143.25± 31.76). The decrease in the serum T_3 levels were found to be statistically significant in both critically ill patients (P<. 001) and severely malnourished patients (P<.01).

   Different hypotheses for decrease serum concentration of T_3 in critically ill and severely malnourished patients have been given by different workers Viz . Impaired thyroid secreation rate low thyrobinding proteins, impaired T_4 monodeiodination in liver due to reduced activity of 5' deiodinase system resulting in a decrease in serum T_3 and increase in serum rT_3 concentrations commonly known as " low T_3 syndrome". Corticosteroids, which are elevated in stress also inhibit T_3 generation from T_4 by inhibiting the 5-deiodinase system.

2. **Thyroxine (T_4):** The mean values of serum T_4 was lower in both study groups (6.59±1.60 in critically ill patients and 7.04 ± 1.26 in severely malnourished patients) as compared to that of control group (8.14±0.67). The decrease in serum T_4 levels were found to be statistically significant in both critically ill patients (P<.01) and severely malnourished patients(P<.02).

   Different hypotheses for decrease serum concentration of T_4 as well as T_3 have been given by different researchers viz- decreased

thyroid secretion rate, decreased serum concentration of thyrobinding proteins like TBG, TBPA and serum albumin, relative iodine deficiency associated with high fecal loss and malabsorbtion of iodine and abnormal thyrotropin secretion.

3. **Thyroid stimulation hormone (TSH)**: The mean serum TSH level was 3.34±1.10 in critically ill patients, 2.12±0.84 in severely malnourished patients and 2.66±0.89 in control group. Statistically significant difference was not observed when study groups were compared to control groups (P>0.1 in both groups).

   Normal TSH level is explained on the basis that as T_4 undergoes intracellular monodeiodination to T_3 at the pituitary level, so central feed back mechanisms are apparently preserved, allowing appropriate adaptation of the thyroid.

CONCLUSIONS

CONCLUSIONS

From the data presented above, the following conclusions may be drawn.

1. Serum total T_3 levels were significantly lower in both critically ill patients and severely malnourished patients ($P<0.001$ & $P<0.01$ respectively).
2. Serum total T_4 levels were significantly lower in both critically ill patients and severely malnourished patients ($P<.01$ & $P<.02$ respectively).
3. Serum TSH levels were not significantly lower in both critically ill patients and severely malnourished patients ($P>0.1$ in both groups).
4. Thus the condition observed by us, "sick euthyroid syndrome" which is characterized by significant decrease in serum triiodothyronin (T_3) and serum thyroxin (T_4) but no significant change in thyroid stimulating hormone (TSH) levels, occurs in all non thyroid illnesses, which have nothing more in common than catabolic state. Hence it has been suggested that the decrease in thyroid hormone level may be a protective phenomenon to limit protein catabolism and lower energy requirements in non thyroidal illnesses.
5. If thyroid indices are measured early in the course of critical illness, which is predictive of subsequent outcome, children with a poor prognosis (low T_3,T_4 levels) could be identified earlier. The clinical value of such laboratory assessment will be enhanced because presumably there will be time available for intensive therapeutic intervention.

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